Addressing the Needs of the High-Risk Prostate Cancer Patient

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For prostate cancer patients with a substantial risk of posttherapy progression, managing the disease with a risk-stratified approach and multimodal therapy is an evolving concept. Through an analysis of prostate-specific antigen (PSA) level, biopsy Gleason score, and clinical stage, investigators have been able to define low-, intermediate-, and high-risk disease in terms of the risk of progression after definitive local therapy. High-risk features include a PSA level greater than 20 ng/mL, a Gleason score of 8 to 10 or a clinical stage of T2c or higher. Because high-risk men treated by surgery or radiation therapy are at increased risk of progression and death from prostate cancer over the ensuing decade, various strategies have been used to improve their rates of disease-free progression and overall survival. Radiation therapy combined with hormonal therapy, radical prostatectomy combined with hormonal therapy or adjuvant radiation, and other approaches, such as chemo-hormonal therapy, are either under study or have been supported in randomized clinical trials. This review summarizes the current standard approaches to treating the man with high-risk disease.
[Rev Urol. *2005;7(suppl 5):S18-S28*]

Key Words: Prostate cancer, high risk • Hormonal therapy • Radiation therapy • Chemo-hormonal therapy

Prostate-specific antigen (PSA) testing has arguably led to most prostate cancers being diagnosed clinically as early, organ-confined disease. More men can now be offered local treatment options, such as radical prostatectomy or radiation therapy (RT). Unfortunately, many patients with clinically localized prostate cancer treated with curative intent can experience PSA (biochemical) progression. This can be due to inadequate primary treatment or unrecognized locally advanced or metastatic prostate cancer. Not all men have an

equal risk of PSA progression after definitive local therapy. We can now identify adverse risk features at the time of diagnosis that might lead to an adverse outcome and stratify patients into risk categories at the time of diagnosis. This so-called "risk-stratified approach" might allow patients to be treated according to their likelihood of recurrence or progression after therapy.

Currently, standard clinical–pathologic correlations seem to be the most useful markers of risk in the man with newly diagnosed prostate cancer, with other more sophisticated markers possible in the future.[1] Clinical stage, serum PSA level, and Gleason score (GS) allow the classification of patients with prostate cancer into the various risk categories.

Several investigators have refined the concept of risk stratification for localized prostate cancer. The stratification schema proposed by D'Amico and associates[2] is the most widely cited. Low-risk patients are those with stage T1c or T2a prostate cancer, PSA level less than 10 ng/mL, or GS less than 6; intermediate-risk patients are those with a GS of 7 or PSA level greater than 10 ng/mL and less than 20 ng/mL; and high-risk patients are those with stage T3a prostate cancer, PSA level greater than 20 ng/mL, or GS greater than 8. In general, patients in the high-risk group are at the greatest risk of progression after standard monotherapy for localized disease (Figure 1).

These data also indicate that men with low-risk features usually do well with standard monotherapy, such as radical prostatectomy or RT (brachytherapy or standard-dose external beam RT [EBRT]). With monotherapy the high-risk patient, identified through adverse clinical features at the time of diagnosis, is more likely to experience treatment failure, defined as PSA progression or the development of clinical metastasis. This places the patient at increased risk of dying from his disease.

Contemporary PSA-based screening might be identifying men earlier in the course of their disease and hence identifying more men with favorable-risk disease. The CaPSURE national database registry supports this observation, having documented a trend of reduced numbers of high-risk prostate cancer patients over the last decade (Figure 2).[3] In 1990, 39% of men had high-risk prostate cancer; by 2003, that number had dropped to 22%.

A variety of tools are now available to more precisely counsel patients as to their outcome with a variety of treatment options and allow risk assessment to be further quantified for an individual patient's unique features. Simple tables, such as those developed by Partin, nomograms, and Internet-based artificial neural networks allow physicians and patients alike to predict outcomes according to specific patient characteristics. An entire issue of *Seminars in Urologic Oncology* has been devoted to the concept of outcomes-based tools, such as nomograms.[4] Validated nomograms as predictive models are now available for prostatectomy,

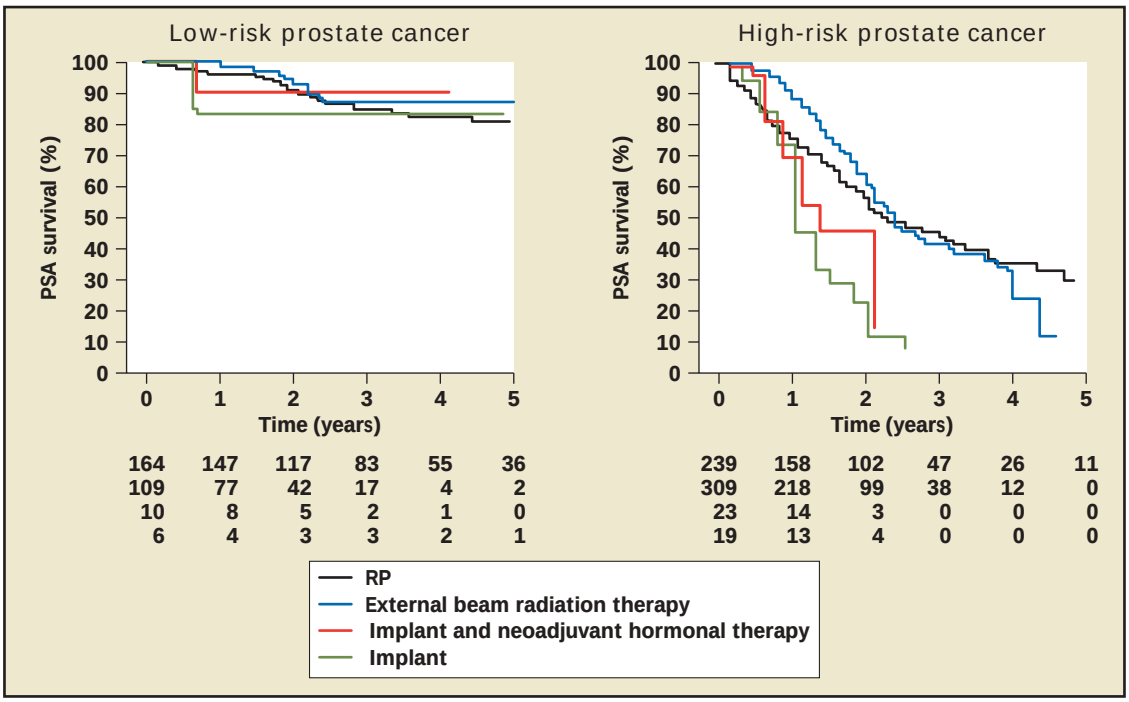

Figure 1. *Prostate-specific antigen (PSA)-based outcomes of low- and high-risk men with localized prostate cancer. RP, radical prostatectomy. Adapted with permission from D'Amico et al.*[2]

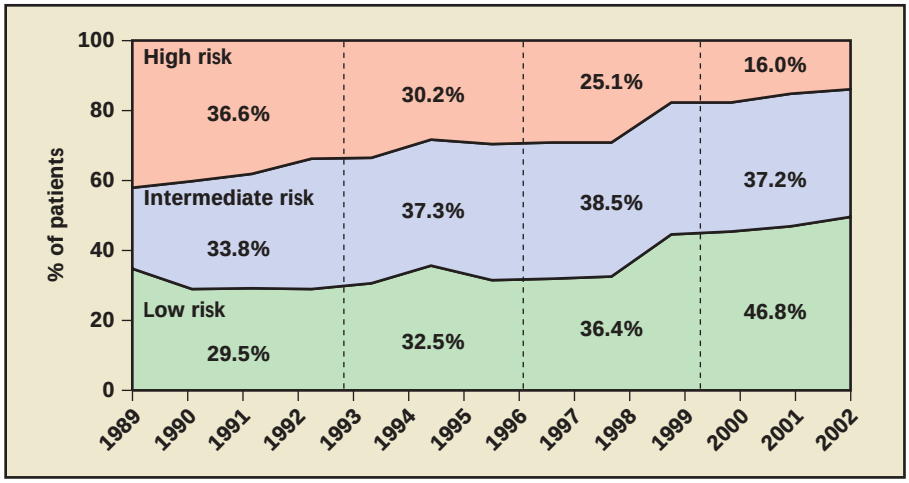

Figure 2. *Changes in risk stratification in patients with newly diagnosed prostate cancer diagnosed in the "PSA era." Reproduced with permission from Cooperberg et al.*[3]

three-dimensional conformal x-ray therapy (XRT), and brachytherapy.[5] Nomograms use algorithms that incorporate several variables to calculate the probability that a patient will achieve a particular clinical endpoint. These validated nomograms outperform both clinical experts and predictive models using methods of risk grouping. These tools might allow identification of individuals who have a high likelihood of progressing or recurring after treatment for localized disease and are useful in the assessment of men with newly diagnosed prostate cancer to help define treatment options.

Although the significance of PSA recurrence after definitive therapy has been debated for years, in high-risk men in particular, rising PSA levels might be associated with prostate cancer–specific death. A study by the British Columbia Cancer Agency[6] found that, in men under 75 years of age with high-risk features treated by RT, PSA recurrence was associated with increased prostate cancer–specific mortality. In men with PSA recurrence and a rapid PSA doubling time, PSA might serve as a surrogate endpoint for overall survival.[7] If one assumes that a rising PSA level is associated with failure of local therapy or systemic progression, it is reasonable to consider additional therapy at the time of definitive therapy, particularly for those individuals at increased risk for recurrence.

Another approach to consider is to initiate therapy at the time of PSA recurrence. There is no consensus at present as to which approach is optimum (ie, the early preemptive treatment based on adverse risk factors or the early initiation of salvage therapy with biochemical or clinical recurrence).[8] This article will focus on various strategies to be used before there is evidence of PSA progression (Table 1).

Other features of the man with high-risk prostate cancer might impact on outcome. Pretreatment PSA velocity might also predict recurrence and death from prostate cancer after definitive local therapy.[9] Biomarkers and nomograms that incorporate other pathologic variables, such as extent of needle core involvement, are under study to more precisely define the patient at risk of local recurrence and/or the development of distant disease.[1]

At present, patients should be classified as having low-, intermediate-, or high-risk disease according to standard clinical variables (GS, clinical stage, and PSA level) incorporated into Partin tables, nomograms, or neural networks. Those at a high risk of failure with monotherapy should be counseled concerning the risks and benefits of various approaches; the first consideration should always be

Table 1
Options for the Management of Localized High-Risk Prostate Cancer

No longer widely used
- Neoadjuvant hormonal therapy before radical prostatectomy

Reasonable options supported by multiple publications
- Radical prostatectomy alone
- Radical prostatectomy with adjuvant radiation therapy
- Radical prostatectomy with adjuvant hormonal therapy
- External beam radiation therapy with hormonal therapy (neoadjuvant, adjuvant alone, and in combination)
- Hormonal therapy alone

Promising or not widely used at present
- "Trimodality therapy" (brachytherapy, external beam radiation, and hormonal therapy)
- Chemo-hormonal therapy with radiation therapy or radical prostatectomy
- Other clinical trials

to incorporate these patients into available clinical trials.

Current data suggest that neoadjuvant hormonal therapy is no longer considered a viable option to improve outcome in high-risk disease.[10] Likewise, routine radioactive seed implantation as monotherapy should not be used in patients with high-risk localized prostate cancer.[2,11] In addition, results from extensive clinical trials (discussed below) indicate that EBRT alone (ie, <72 Gy) also should not be considered an option, until the results of dose escalation and other external beam enhancements are clearly defined.

Current commonly used "standard" options that should be considered when making treatment recommendations for men with high-risk prostate cancer include the following:

- Radical prostatectomy
- Radical prostatectomy and adjuvant RT
- Radical prostatectomy and adjuvant hormonal therapy
- External beam radiation with hormonal therapy
- Hormonal monotherapy
- Other approaches: clinical trials, trimodality therapy, adjuvant chemohormonal therapy

Radical Prostatectomy

There have been well-documented changes in pathologic outcomes of contemporary radical prostatectomy.[12] Although many men are classified as "high risk" on the basis of the features described above, the inherent changes in PSA-based screening are leading to the diagnosis of earlier-stage disease and fewer men with high-risk disease.

As monotherapy, radical prostatectomy alone can be considered in some high-risk patients. In one review of 190 men with clinically localized high-risk disease (ie, GS > 8), 55 men (29%) had organ-confined disease, 48 (25%) were T3 margin negative, and 22 (12%) had T3 margin-positive disease.[13] With a 5-year median follow-up, the 5- and 7-year disease-free survival rates were 81% and 68%, respectively. In this high-risk group with a median follow-up of 60 months, 79.5% exhibited no evidence of disease (NED). When additional features are included beyond high Gleason grade, failure rates at 5 years can exceed 50%. In men with extracapsular extension, the 5-year rates of biochemical non-evidence of disease (bNED) range from 27% to 79%; when extracapsular extension is associated with a positive margin, the rates range from 26% to 66%.[14]

In a related study of high-risk prostate cancer, of 79 men with a GS of 8 on biopsy, 25 (31%) were found to have been over-scored (GS of ≤ 7) at radical prostatectomy pathologic evaluation.[15] PSA failure was 41% if the final GS was 8 or higher, with 20% of patients (11 of 54) having organ-confined disease. These investigators indicated that radical prostatectomy is a reasonable treatment option for patients with a prostate biopsy GS of 8 or more.

Taken together, these data from contemporary reports on radical prostatectomy suggest that a group of men with adverse features on biopsy might do well after radical prostatectomy alone. This might be owing to "downgrading" at the time of whole prostate pathology or to the fact that the "adverse" features on the initial biopsy are low volume and perhaps not as aggressive as higher-volume disease. However, a significant number of men will manifest progression and should be considered for additional, multimodality therapies. In a man with high-risk features who elects radical prostatectomy, counseling should include a reasonable discussion of expected outcomes based on nomograms or other tools. The potential need for additional therapy postoperatively should be made clear to the patient. Again, tools might be more robust in the postprostatectomy setting and allow more accurate outcome assessments. This discussion should include full disclosure that the optimum adjuvant regimen, should final pathology results suggest one might be needed, is not known at present.

Adjuvant Postoperative Radiation Therapy

Whether postoperative RT should be used after radical prostatectomy (and if so, when) has been a longstanding controversy. A challenge is that a clear-cut survival advantage has not been demonstrated in the adjuvant setting. When patients are found to have pT2N0 prostate with negative margins, the long-term progression-free survival rate is as high as 84% to 98%. If pathologically the disease extends beyond the prostatic capsule (pT3) or is present at the surgical margins, disease-free survival is lower (37%–70%), suggesting a subclinical disease burden.[16] For these patients, the role of adjuvant therapy, whether hormonal therapy or RT, remains controversial and is the subject of several important prospective randomized trials.

Postoperative RT has been used in the PSA recurrence and adjuvant setting. For adjuvant RT, the goal is to increase local tumor control by eradicating microscopic residual tumor in the periprostatic tissues or adjacent pelvic lymph nodes.[17-19]

There is significant controversy as to whether early adjuvant RT improves overall survival in men with locally advanced disease (pT3) with or without positive surgical margins. Data have been published regarding the administration of radiation in the high-risk setting with undetectable PSA levels (adjuvant pT3); these are summarized in Table 2.

Table 2
Selected Series of Adjuvant Radiation Therapy for T3N0M0 Prostate Cancer Compared With a Control Group

First Author	No. of Patients	Radiation Dose (Gy)	Progression-Free Survival	Follow-Up (mo)
Gibbons[47]	23	None	70% NED, local 65% NED, distant	94
	23	49–72 Gy	95% NED, local 77% NED, distant	57
Morgan et al.[48]	33	None	64% bNED	11
	17	60–66 Gy	94% bNED	
Anscher et al.[49]	46	None	60%	120
	113	55–65 Gy	68%	
Stein et al.[50]	91	None	43% bNED	48
	24	55–60 Gy	75% bNED	
Schild et al.[51]	228	None	40% bNED	32
	60	57–68 Gy	57% bNED	
Valicenti et al.[52]	36	None	55%	41
	36	59.4–70.2 Gy	88%	

NED, no evidence of disease; bNED, biochemical NED.

One study[17] reported that patients receiving postoperative irradiation had reduced mortality when compared with men having no immediate therapy. In a re-analysis of the same data set with extended follow-up, no survival benefit was noted.[20] In a further publication from the same group, a significantly better (67%) 10-year disease-free survival and fewer distant metastases were reported for men with positive margins who were irradiated postoperatively, compared with patients not irradiated (30% 10-year disease-free survival). Anscher and colleagues[21] updated their report on 159 patients who underwent radical prostatectomy and were found to have pathologic stage T3/4 tumors; 46 patients received adjuvant RT (total dose of 55–65 Gy), and 113 did not. Both groups of patients were followed for a median of 10 years. The disease-free survival rates for the RT group were 55% and 48% at 10 and 15 years, respectively, compared with 37% and 33% for the radical prostatectomy–alone group ($P = .16$). The actuarial survival rate was 52% at both 10 and 15 years for the RT group, compared with 52% and 37% for the radical prostatectomy–alone group ($P = .18$).

Matched-pair analyses of patients undergoing postoperative RT have been conducted by several groups.[22,23] At Thomas Jefferson University, a series of 149 patients who had pathologic T3N0 prostate cancer with undetectable postoperative PSA level underwent radical prostatectomy; 52 received adjuvant RT within 3 to 6 months after surgery, and 97 underwent radical prostatectomy alone until a PSA failure was noted.[22] All patients were matched according to prognostic factors. The 5-year rate of freedom from PSA relapse was 89% for patients receiving adjuvant RT, compared with 55% for those with radical prostatectomy alone ($P < .01$) (Figure 3). Another retrospective analysis[23] concerned 76 men with pathologic stage T2N0 prostate cancer and a single positive margin who underwent postoperative RT within 3 months of radical prostatectomy and 76 control patients with similar characteristics who did not receive adjuvant RT. There was a higher 5-year clinical and biochemical progression-free survival rate (88% versus 59%) in patients irradiated versus patients not receiving RT. No patient treated with

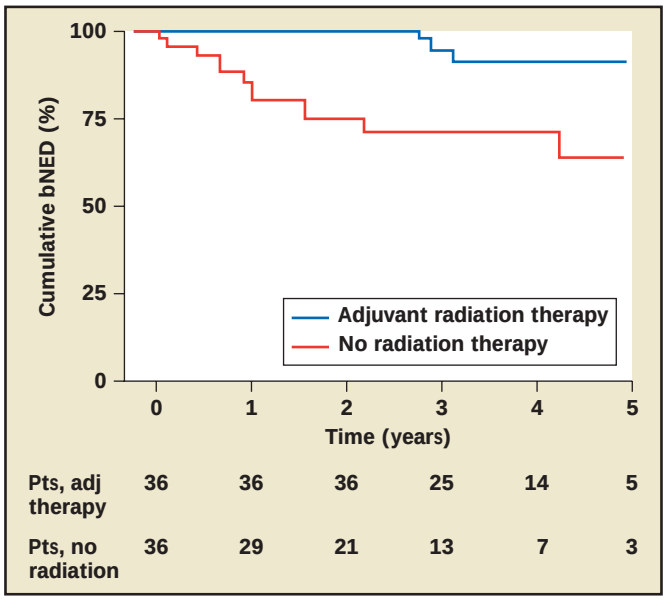

Figure 3. *Results of adjuvant radiation therapy in a group of high-risk men with postoperative prostate-specific antigen (PSA) levels of less than 0.2 ng/mL and matched controls followed with observation. bNED, biochemical non-evidence of disease. Reproduced with permission from Valicenti et al.*[22]

postoperative radiation developed a local or distant recurrence, whereas 16% of the control group did have a recurrence ($P = .015$).

Seminal vesicle invasion traditionally has been equated with distant disease, and therefore local salvage radiation was not considered useful. In a single-institution review of seminal vesicle involvement with negative nodes,[24] results were encouraging. Patients who received adjuvant RT had significantly greater 5-year bNED survival than patients who did not (80% vs 8%, $P < .001$), and increased freedom from prostate cancer death was of borderline significance ($P = .05$). The 5-year survival estimate for prostate cancer death was 0% for the adjuvant RT group, compared with 17% for the observed patient group.

A recently reported European Organization for Research and Treatment of Cancer (EORTC) prospective randomized trial[25] attempted to answer this question in a phase 3 trial. In this trial, 1005 men with high-risk features after radical prostatectomy for clinically localized disease were randomized to 60 Gy adjuvant radiation versus observation. Clinical progression-free survival improved from 74.8% to 83.3% in the radiation arm, with a highly statistically significant decline in local failure. Toxicity was minimal, and further follow-up is needed to determine the ultimate effect on survival. Another study, Southwest Oncology Group 9024, was a phase 2 study of combined modality therapy with adjuvant RT in T3 and T4 prostate cancer; it is closed and is in follow-up.[26] It is important to note that the doses of pelvic RT in these trials might be less than is used today.

Salvage radiation can be used in the high-risk patient who has a PSA relapse; however, there is a growing body of evidence that the use of salvage radiation in patients with rising PSA levels after radical prostatectomy should be initiated at the lowest PSA level possible. For example, in a recent multi-institutional analysis of salvage RT for PSA failure after radical prostatectomy, the results were improved if the RT was administered when the PSA level was less than 2.0 ng/mL.[27] Lower disease burden might enhance the effect of radiation in this setting, and as such, adjuvant radiation attempts to treat minimal postoperative disease.

Technical considerations are important with respect to postoperative RT. Higher RT doses have been shown to reduce the risk of both clinical and biochemical failure as compared with lower doses in the intact prostate. For patients with an increased risk of local failure after radical prostatectomy, a similar RT dose–response relationship might also exist. In a report by Schild and colleagues,[28] patients who received more than 64 Gy had a 30-month freedom from failure of 62%, compared with 17% for patients who had a lower dose ($P = .03$). Others have reported a postoperative RT dose response. In the group of adjuvant patients, those who received more than 61.2 Gy had a 4-year bNED survival rate of 95%, compared with 68% for those who had a lower radiation dose ($P = .015$).[22] These data suggest that a dose that approaches the intact prostate treatment plan should be used in the postoperative setting. All studies reported above suggest that acute and long-term toxicity is minimal with the use of contemporary targeting techniques.

Adjuvant Postoperative Hormonal Therapy

Most reports of postoperative hormonal therapy are single institution reviews.[29] The Early Prostate Cancer study is a large trial involving more than 8000 men with localized prostate cancer who received bicalutamide 150 mg orally daily as an adjuvant strategy after definitive treatment or with watchful waiting.[30] For the entire group, the use of bicalutamide 150 vs. placebo reduced the objective and PSA progression for all disease categories. For the European post–radical prostatectomy population, patients with a GS greater than 7 and a baseline PSA level greater than 10 ng/mL, irrespective of T-stage (ie, intermediate- and high-risk disease), derived a significant benefit in terms of PSA and objective progression. Outcomes in the United States radical prostatectomy population are not yet significant and continue in follow-up.

Although technically a "node positive" intervention, the Messing/Eastern Cooperative Oncology Group study (ECOG 3886) lends itself well to the discussion of adjuvant hormonal therapy after radical prostatectomy. It stands as the only randomized prospective study of early versus delayed adjuvant hormonal therapy after radical prostatectomy and bilateral pelvic lymphadenectomy with long enough follow-up to assess its influence on survival.[31] ECOG 3886 limited itself to patients with clinically localized disease who were found on permanent pathologic inspection to have nodal metastases. The majority had cancers with pathologic extraprostatic extent and GS greater than 7. In this study, 98 men were randomized to immediate and continuous hormonal monotherapy (luteinizing hormone-releasing hormone [LHRH] agonist or bilateral orchiectomy) versus hormonal therapy upon disease progression (almost always bony metastases). At 7.1 years median follow-up, immediately treated patients had significantly better overall survival (85.1% vs 64.7%, $P = .02$) and disease-specific survival (93.6% vs 68.6%, $P < .01$), and only 16% of men in the deferred arm were

alive without at least biochemical recurrence. Adjuvant hormonal therapy can be considered in certain high-risk men after radical prostatectomy as an alternative treatment regimen.

Adjuvant Radiation Therapy Combined With Hormonal Therapy

It is recognized that there are significant advantages to combining hormonal therapy in the setting of EBRT primarily seen in the high-risk patient. The issue of adding hormonal therapy in the post–radical prostatectomy adjuvant radiation setting has been addressed in several recent reports. The practice represents a standard of care for high-risk men who choose RT as their primary treatment option.

One retrospective, single-institutional analysis suggests that there might be a survival advantage to this combined approach in the postoperative setting.[32] A total of 122 patients received RT after radical prostatectomy, with 53 receiving short-course total androgen ablation 2 months before and 2 months concurrent with RT. The median time to PSA failure after postoperative RT was 1.34 years for the combined therapy group and 0.97 years for the RT-alone group ($P = .19$), with no failures beyond 5 years. At 5 years, the actuarial bNED rates were 57% for the combined therapy group, compared with 31% for the RT-alone group ($P = .0012$). Overall survival rates at 5 years were 100% for the combined therapy group, compared with 87% for the RT-alone group ($P = .0008$). For pathologic GS of 7, the 5-year bNED rates were 58% for combined therapy and 38% for RT alone ($P = .0155$), and for a GS of 8 the 5-year bNED rates were 65% for combined therapy and 17% for RT alone ($P = .075$). The 5-year overall survival rates for a GS of 7 were 100% for combined therapy and 98% for RT alone group ($P = .106$), and the 5-year overall survival rate for a GS of 8 was 100% for combined therapy and 54% for RT alone ($P = .04$). This study suggests that postoperative RT combined with a short course of androgen ablation confers a PSA relapse-free survival advantage and possibly an overall survival advantage when compared with RT alone. The benefits were most pronounced in the high-risk patients. A limitation to this approach is that the effect of radiation treating only localized disease cannot be differentiated from the possible systemic effect of hormonal therapy of distant disease.

Radiation Therapy and Hormonal Therapy

Large, prospective, randomized trials combining EBRT and hormonal therapy in the adjuvant and neoadjuvant setting have confirmed the utility of this approach in many patients.[33] It is becoming apparent, however, that not all patients benefit from this approach. Long-term androgen ablation (2 to 3 years) currently is considered essential in high-risk disease and can lead to an overall survival advantage when compared with RT alone. Furthermore, the addition of pelvic nodal radiation combined with hormonal therapy benefits men at high risk for pelvic lymph node involvement, with the best outcomes when the hormonal therapy is used neoadjuvantly and on treatment.[34]

Patients with low- and intermediate-risk disease might not enjoy the same benefit from the use of androgen ablation because no definitive randomized trials have clearly demonstrated an improved outcome.[35] Many trials have addressed the combined hormonal and EBRT approach to prostate cancer (reviewed by Sandler[33]). Several studies are worthy of highlighting because they have significantly influenced how RT is administered today, particularly in the man with high-risk prostate cancer.

The Bolla/EORTC 22863 study was a multicenter trial in which 1 month of neoadjuvant hormonal therapy was used before XRT, followed by 3 years of LHRH in patients with mostly bulky local disease (ie, T3 and T4, high risk). Improved rates of local control, disease-free survival, and overall survival were noted at 5 years.[36,37] This was the first study of localized prostate cancer that demonstrated an improvement in overall survival in the treatment arm.

Radiation Therapy Oncology Group (RTOG) 92-02 was a randomized trial of long-term adjuvant androgen deprivation after initial androgen deprivation with XRT in high-risk patients with locally advanced prostate cancer (T2c-4) and a PSA level less than 150 ng/mL.[38] Patients received a total of 4 months of goserelin and flutamide, 2 months before and 2 months during RT. A radiation dose of 65 to 70 Gy was given to the prostate and a dose of 44 to 50 Gy to the pelvic lymph nodes. Patients were randomly assigned to receive no additional therapy (short-term androgen deprivation [STAD]-RT) or 24 months of goserelin (long-term androgen deprivation [LTAD]-RT); 1554 patients were entered into the study. The LTAD-RT arm showed significant improvement in all efficacy endpoints

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except overall survival (80.0% vs 78.5% at 5 years, $P = .73$) compared with the STAD-RT arm. In a subset analysis of patients with GS of 8 to 10, the LTAD-RT arm fared significantly better overall (81.0% vs 70.7%, $P = .044$). This trial also supports the addition of long-term adjuvant androgen deprivation to short-term adjuvant androgen deprivation with radiation for bulky disease (T2c-4). In the subset analysis of the highest-risk patients, with GS 8 to 10, long-term adjuvant androgen deprivation resulted in a survival advantage.

RTOG 9413 tested the hypothesis that total androgen ablation and whole-pelvic RT followed by a boost to the prostate improves progression-free survival in 1323 men.[34] This trial also tested the hypothesis that neoadjuvant and concurrent hormonal therapy improves progression-free survival compared with adjuvant hormonal therapy. It included a group of very-high-risk patients with a risk of nodal metastasis of greater than 15%. Eligibility included localized prostate cancer, an elevated PSA level of 100 ng/mL or less, and an estimated risk of lymph node involvement of 15%. Patients were randomly assigned to whole-pelvic RT + neoadjuvant and concurrent hormonal therapy; prostate-only RT + neoadjuvant and concurrent hormonal therapy; whole-pelvic RT + adjuvant hormonal therapy; or prostate-only RT + adjuvant hormonal therapy. With a median follow-up of 59.5 months, whole-pelvic RT was associated with a 4-year progression-free survival of 54%, compared with 47% in patients treated with prostate-only RT ($P = .022$). Patients treated with neoadjuvant and concurrent hormonal therapy experienced a 4-year progression-free survival of 52%, compared with 49% for patients receiving adjuvant hormonal therapy ($P = .56$). No survival advantage has been seen in a relatively short follow-up. These results from RTOG 9413 suggest that whole-pelvic RT + neoadjuvant and concurrent hormonal therapy improves progression-free survival compared with prostate-only RT and neoadjuvant and concurrent hormonal therapy or prostate-only RT and adjuvant hormonal therapy, and compared with whole-pelvic RT + adjuvant hormonal therapy in high-risk patients with a risk of lymph node involvement of greater than 15% (Figure 4).

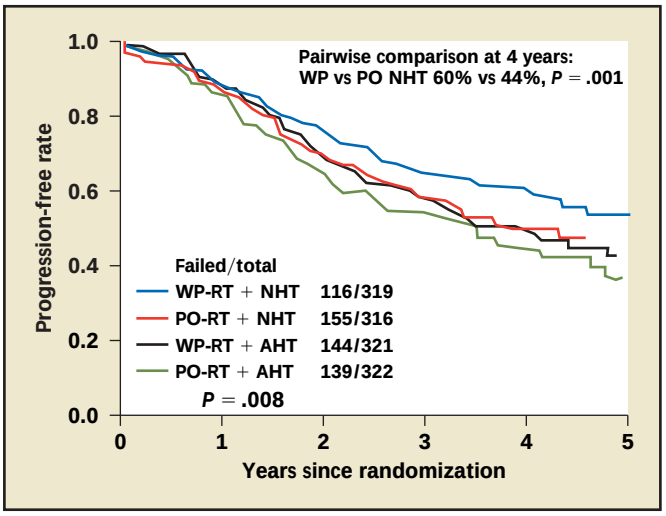

Figure 4. *Results of Radiation Therapy Oncology Group study 9413. High-risk patients who received whole-pelvic radiation therapy (WP-RT), including prostate and lymph nodes, along with neoadjuvant hormonal therapy (NHT) had improved prostate-specific antigen recurrence rates compared with the other groups. PO-RT, prostate-only radiation therapy; AHT, adjuvant hormonal therapy. Reproduced with permission from Roach et al.*[34]

These and other studies strongly suggest that combined hormonal therapy and EBRT should be used in high-risk patients who elect no surgical primary treatment. What is still not clear is the timing and duration of the therapy. A study from Boston was the first to suggest that 6 months of androgen deprivation would be acceptable in intermediate- and high-risk men.[39] At present, the majority of the data suggest that long-term hormonal therapy (2 to 3 years) should be considered for most high-risk men until further studies support the use of a shorter duration.

Hormonal Therapy Only in High Risk Prostate Cancer

In the absence of documented advanced disease, hormonal therapy has not been widely studied in an organized fashion to determine the ultimate outcomes. In a retrospective analysis comparing radical prostatectomy with primary endocrine therapy, no difference in outcomes was apparent at 5 years.[40] The investigators note that endocrine therapy offers a reasonable survival rate in T1b-T3 prostate cancer patients within a 5-year follow-up period.

Despite the lack of extensive data for the use of hormonal therapy as a primary intervention, its use is increasing. According to the CaPSURE database, the use of hormonal therapy as a primary therapy for high-risk men increased from 17% in 1990 to 33% in 2003.[41] The use of hormonal therapy alone is an option for patients with high-risk disease. This approach might treat the localized disease as well as any disease outside the prostate. The potential side effects of long-term androgen ablation must be considered when making this recommendation. Continuous treatment is probably best until more data are available regarding the use of intermittent therapy in prostate cancer.

Other Promising Approaches

Trimodality Therapy

Limited studies have addressed the use of EBRT and hormonal therapy in prostate cancer. Stock and associates[42] studied the efficacy of a multimodality protocol using neoadjuvant and concomitant hormonal therapy, brachytherapy, and three-dimensional conformal EBRT in high-risk prostate cancer. They found that the rate of actuarial overall freedom from PSA failure was 86% at 5 years. The rate of freedom from PSA failure at 5 years was 97% for those with a GS of 6 or less (35 of 36), 85% for a GS of 7 (50 of 59), and 76% for a GS of 8 to 10 (28 of 37, $P = .03$). A trend was noted toward worse outcomes in seminal vesicle biopsy–positive patients, with a 5-year rate of freedom from PSA failure of 74%, compared with 89% for all other patients ($P = .06$). For these investigators, this approach was considered to be an acceptable treatment modality for this patient population.

Adjuvant and Neoadjuvant Chemo-Hormonal Therapy and Radical Prostatectomy

Interest in the use of adjuvant chemo-hormonal therapy has increased since the approval of docetaxel for advanced hormone refractory prostate cancer.[43] Several active trials are attempting to address this important question.[44] At present, however, this approach should only be performed in the context of a clinical trial. A recent multicenter trial, RTOG 9902, in which high-risk men were treated with chemo-hormonal therapy and RT, was forced to close owing to chemotherapy-related toxicity.[45] The study is being revised to include newer agents, such as docetaxel.

Clinical Trials

With the recognition that it is the circulating micrometastasis that ultimately leads to the death of men with high-risk disease, a variety of new creative strategies are under development and offer hope for the future.[46] Physicians should be aware that there are many clinical trials testing new compounds in their local communities and attempt to place appropriate men on these important studies.

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Conclusions

In meeting the needs of the patient with high-risk prostate cancer today, the multimodality approaches available must be presented to the patient in an objective fashion. The optimum treatment approach is unknown at

Main Points

- Assessment of the individual risk status of each patient is now essential in the successful treatment of localized prostate cancer; high-risk patients should be considered for randomized clinical trials as a primary option.
- Extensive data to indicate that multimodality therapy, combining surgery, radiation, and hormonal and chemotherapy approaches, might have a role in the management of men at increased risk for recurrence.
- Postoperative radiation therapy (RT) has been used in the PSA recurrence and adjuvant setting; there is significant controversy as to whether early adjuvant RT improves overall survival in men with locally advanced disease with or without positive surgical margins.
- Adjuvant hormonal therapy can be considered in certain high-risk men after radical prostatectomy as an alternative treatment regimen.
- A retrospective, single-institutional analysis suggests that postoperative RT combined with a short course of androgen ablation confers a PSA relapse-free survival advantage compared with RT alone, with benefits being most pronounced in high-risk patients.
- Studies strongly suggest that combined hormonal therapy and external beam RT should be used in high-risk patients who elect no surgical primary treatment; the optimal timing and duration of the therapy remain unclear.
- The use of hormonal therapy alone is an option for patients with high-risk disease; the potential side effects of long-term androgen ablation must be considered, and continuous treatment is probably best until more data are available regarding the use of intermittent therapy in prostate cancer.

present. Although new approaches, such as chemo-hormonal therapy, are encouraging, patients must make treatment decisions on the basis of the best currently available data.

Assessment of the individual risk status of each patient is now essential in the successful treatment of localized prostate cancer. Treatment options should be carefully reviewed with each patient on an individualized basis. High-risk patients should be considered for randomized clinical trials as a primary option. There are extensive data to indicate that multimodality therapy, combining surgery, radiation, and hormonal and chemotherapy approaches, might have a role in the management of the men with this potentially life-threatening disease. ■

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